

makes November 19, 2005 the due date for response instead of August 19, 2005.

Also submitted herewith is the Declaration of Xiaoyong Fu setting forth the purity of Furan XI obtained in Preparative Example 1 (Scheme III) of the above identified Application.

Also submitted herewith is a supplemental Information Disclosure Statement.

The Rejection

Claims 1-31, 43-54 and 66-81 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Taveras et al. (WO 02/083624) in view of Miao et al. for the reasons of record.

Applicants respectfully traverse this rejection.

The cited references do not teach, disclose or suggest Applicants' claimed invention.

Taveras et al. disclose a method of making the compound of formula I (see page one of the above identified Application and the present Office Action) using valinol as stated in the Office Action. Valinol is used in the preparation of the furan amine from the furan aldehyde (see Preparative Example 75.1 on page 178 with reference to Preparative Example 64 on page 174, for example) .

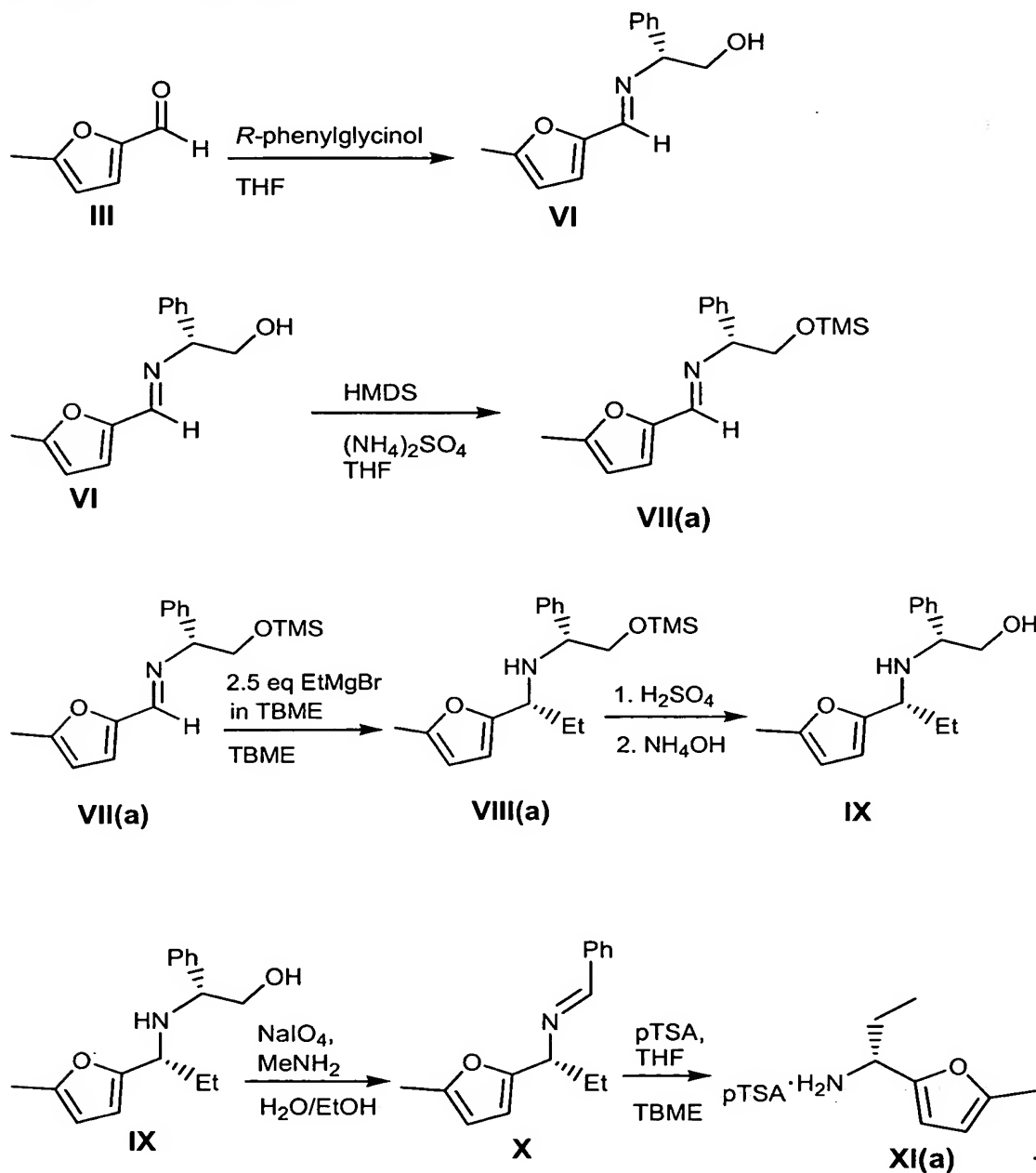
Miao et al. disclose a reaction (see page 2259, Scheme 1) wherein a pyridyl amine is prepared from valinol (Y is isopropyl) or phenylglycinol (Y is phenyl). The reaction with valinol (Y is isopropyl) produces intermediates 3a and 3b in a diastereomeric ratio of 87:13 of 3a:3b. This mixture was oxidatively cleaved with NaIO₄ to a 75% ee based on chiral HPLC results.

Miao et al. do not report results when phenylglycinol (Y is phenyl) is used in the reaction in Scheme 1.

In Scheme 2 of Miao et al. the reaction of a pyridine ketone (4) with, for example, R-phenylglycinol is disclosed. The reaction product is catalytically reduced to produce compounds 6a and 6b in a ratio of 98:2.

Oxidative cleavage of these diastereomers with NaIO_4 yields the desired amine **1a** with a 96% ee (based on chiral HPLC). These results show that both the desirable diastereomer and the undesirable diastereomer are oxidatively cleaved.

Applicants' claimed process includes the preparation of furan imine **X** from the furan aldehyde **III**; then Furan imine **X** is converted to Furan amine **XI**. This process is exemplified in Applicants' Scheme III (Preparative Example 1):



In Applicants' Preparative Example 1, the Furan aldehyde III is reacted with phenylglycinol to obtain Furan VI.

Furan VI is then protected to yield Furan VII(a) which is then reacted with the organometallic (EtMgBr) reagent to produce Furan VIII(a).

Furan VIII(a) is obtained as a mixture containing about 90% of the desired (R,R) diastereomer and about 10% of the undesired (R,S) diastereomer.

Furan VIII(a) is then deprotected to yield Furan IX.

Furan IX is then subjected to oxidative cleavage with NaIO₄ to produce Furan imine X.

Furan imine X is then treated with acid (pTSA) to produce Furan amine XI(a).

In Applicants' claimed process, only the desired (R,R) diastereomer is oxidatively cleaved. The undesired (R,S) diastereomer, according to HPLC analysis, remains unreacted.

Because only the desired (R,R) diastereomer is cleaved, Furan XI(a) is formed in a >99% ee after the Furan imine X is treated with acid (pTSA).

Miao et al. teach that the use of valinol in their Scheme 1 produces a product with a purity of only 75% ee. Miao et al. teach that the use of R-phenylglycinol in Scheme 2 produces a product with a 96% ee. These results show that both the desirable and undesirable diastereomers are being oxidatively cleaved.

Thus, Applicants' claimed process surprisingly and unexpectedly yields Furan amine XI(a) in a purity of >99% ee.

Therefore, the combination of references does not render Applicants' claimed invention obvious.

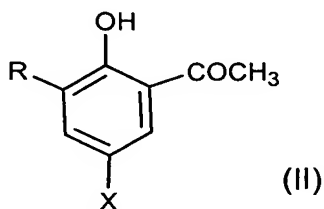
The Examiner is requested to reconsider and withdraw this rejection.

Form PTO/SB/08a or 08b

Higashiyama et al., Tetrahedron Letters, Vol. 33, No. 2, pp. 235-238 disclose the reaction of MeLi or MeMgBr with chiral imines and 2-aryl-1,3-oxazolidines derived from (R)-phenylglycinol. The aryl portion of Compound 3(c), on page 236 (Scheme 1 and Table 1), is a 2-furyl group.

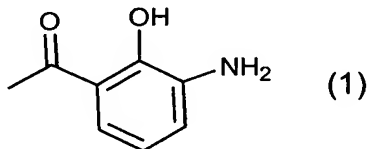
Scheme 2 and Table 2 on page 237 disclose the formation of product 5(c) from the reaction of 3(c) and MeLi. According to Table 2, the ration of isomers R,R:R,S was 95:5.

The abstract for Japanese 11-29540 discloses a compound of the formula:

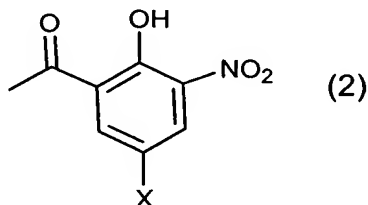


wherein R is $-\text{NO}_2$ and X is halo.

GB 2298861 discloses a process for producing crystals of 3-amino-2-hydroxyacetophenone salt by treating 3-amino-2-hydroxyacetophenone of the formula:

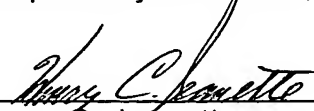


or a hydrogen halide salt thereof with sulfuric acid, in a solvent. The reference discloses that 3-amino-2-hydroxyacetophenone hydrochloride can be used. The reference also discloses that the compound (1) can be obtained by reducing the compound of formula (2):



(wherein X represents a halogen atom or a hydrogen atom) in the presence of a catalyst.

Respectfully submitted,


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